

Blood-Brain Barrier Disruption and Intra-Arterial Methotrexate-Based Therapy for Newly Diagnosed Primary CNS Lymphoma: A Multi-Institutional Experience

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ABSTRACT

Purpose

Primary CNS lymphoma (PCNSL) is confined to the CNS and/or the eyes at presentation and is usually initially treated with intravenous methotrexate-based chemotherapy and whole-brain radiotherapy (WBRT). However, the intact blood-brain barrier (BBB) can limit diffusion of methotrexate into brain and tumor. With BBB disruption (BBBD), enhanced drug delivery to the tumor can be achieved.

Patients and Methods

This report summarizes the multi-institutional experience of 149 newly diagnosed (with no prior WBRT) patients with PCNSL treated with osmotic BBBD and intra-arterial (IA) methotrexate at four institutions from 1982 to 2005. In this series, 47.6% of patients were age ≥ 60 years, and 42.3% had Karnofsky performance score (KPS) less than 70 at diagnosis.

Results

The overall response rate was 81.9% (57.8% complete; 24.2% partial). Median overall survival (OS) was 3.1 years (25% estimated survival at 8.5 years). Median progression-free survival (PFS) was 1.8 years, with 5-year PFS of 31% and 7-year PFS of 25%. In low-risk patients (age < 60 years and KPS ≥ 70), median OS was approximately 14 years, with a plateau after approximately 8 years. Procedures were generally well tolerated; focal seizures (9.2%) were the most frequent side effect and lacked long-term sequelae.

Conclusion

This large series of patients treated over a 23-year period demonstrates that BBBD/IA methotrexate-based chemotherapy results in successful and durable tumor control and outcomes that are comparable or superior to other PCNSL treatment regimens.

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INTRODUCTION

The incidence of primary CNS lymphoma (PCNSL) in immunocompetent patients represents approximately 4% of intracranial neoplasms. This aggressive, extranodal non-Hodgkin's lymphoma is confined to the CNS and/or the eyes at presentation. Patients age ≥ 60 years account for more than 50% of the cases.¹

Numerous studies suggest high-dose methotrexate ($\geq 1 \text{ g/m}^2$), despite its modest blood-brain barrier (BBB) permeability (approximately 5% of plasma levels),^{2,3} combined with brain irradiation results in improved patient response and prolonged progression-free survival (PFS) and overall survival (OS).⁴⁻⁸ Combined-modality therapy, however, is associated with a high incidence of delayed and often

devastating neurocognitive toxicity in long-term survivors, especially those older than 60 years.^{4,9-20}

We update our previously reported single-center results^{21,22} and present our large multi-institutional experience in the treatment of patients with PCNSL using BBB disruption (BBBD) in conjunction with intra-arterial (IA) methotrexate-based chemotherapy. We report for the first time the PFS in this large series, as well as OS and toxicity. This series is unique in that patients were treated over a 23-year period.

PATIENTS AND METHODS

Patients

Newly diagnosed immunocompetent patients with PCNSL (n = 131) were enrolled onto the study and

prospectively treated by the BBBB programs at four institutions (Oregon Health & Science University, Portland, OR; Cleveland Clinic, Cleveland, OH; Hadassah Hebrew Medical Center, Jerusalem, Israel; and Ohio State University, Columbus, OH) between February 1982 and December 2005. Eligible patients had histologically confirmed PCNSL (by brain biopsy, CSF cytology, or vitrectomy), with no evidence of lymphoma elsewhere in the body and no HIV infection at diagnosis. Before treatment, patients were required to have an absolute granulocyte count more than $1,200/\mu\text{L}$, platelet count more than $100,000/\mu\text{L}$, and normal hepatic and renal function. Patients with uncontrolled pulmonary or cardiac complications were not eligible. Uniform protocols were approved by the local institutional review board (IRB) or ethics committee of each institution. Informed consent was obtained from the patients. Newly diagnosed patients (ie, those within 90 days of histologic diagnosis) and those who had not received prior whole-brain radiotherapy (WBRT) are included in this report.

In addition, each institution obtained IRB permission to include newly diagnosed patients with PCNSL ($n = 18$) treated off-protocol with methotrexate-based chemotherapy between the same dates and institutions who met the following criteria: no systemic lymphoma or HIV at diagnosis and no prior WBRT. Therefore, although the vast majority of the patients (131 of 149; 88%) were enrolled onto a prospective study, results from all patients treated with BBBB at the four institutions between 1982 and 2005 who met the above criteria are included in this report, whether treated on or off protocol.

Pre-treatment studies included physical examination, Karnofsky performance score (KPS), cranial magnetic resonance imaging with and without contrast, and extraneural computed tomography staging (chest and abdomen). Before magnetic resonance imaging availability, cranial computed tomography scans were obtained. Bone marrow biopsy and ophthalmologic examination with slit lamp evaluation were performed as indicated, and CSF cytopathology was obtained if lumbar puncture could be safely performed.

Treatment

Chemotherapy protocols were uniform across the four BBBB consortium institutions. Comprehensive guidelines for anesthesia, transfemoral arterial cannulation, mannitol/chemotherapy infusion, pre- and post-BBBB patient care, and follow-up were centrally developed and followed by trained teams at all institutions.

Osmotic BBBB with IA infusion of methotrexate-based chemotherapy has been described previously.²¹⁻²⁴ The BBBB and chemotherapy treatment details are summarized in Table 1. The treatment of intraocular lymphoma included intraocular methotrexate²⁵ or ocular radiation. Leucovorin rescue (80 mg intravenously [IV]) was initiated 36 hours after the first dose of methotrexate and continued thereafter for 5 days (50 mg, orally or IV, every 6 hours).^{21,24,26} Patients received two BBBB treatments on 2 consecutive days every 4 weeks for up to 12 monthly courses unless there was evidence of disease progression.^{21,24}

Response Evaluation and Follow-Up

Follow-up studies included complete neurologic examinations, CBCs, ophthalmologic examination, and CSF cytopathology. Neuroimaging studies were obtained before each monthly treatment course, after the final treatment course, and thereafter every 3 months for 1 year, every 6 months for 2 years, and then annually. Standard parameters were used to determine treatment response.²⁷ For instance, a complete response (CR) was documented if there was complete resolution of enhancing abnormalities on imaging, no evidence of active ocular lymphoma, negative CSF cytology with absence of leptomeningeal disease-related symptoms, and no corticosteroids.

Standard data collection forms and BBBB chemotherapy records were sent to the BBBB coordinating center (Oregon Health & Science University) for review and database entry. Data were reviewed for correctness by each institution and centrally. Data was collected through December 2005. Protocol adherence was overseen by the IRB, and quality assurance audits began in 1996 with the establishment of a cancer center at the BBBB coordinating center.

Statistical Methods

Demographic, baseline, and treatment characteristics were summarized using descriptive statistics. Complications were summarized as both proportion of patients with each complication, the total number of episodes, and the

Table 1. Blood-Brain Barrier Disruption Treatment

Day	Treatment
Day 1, admission	History and physical examination Routine labs Neuroimaging
Days 2 and 3	BBBD treatment General anesthesia Antiepileptic drugs Transfemoral catheterization of carotid or vertebral artery 25% warmed mannitol IA infusion over 30 seconds IV imaging agent Chemotherapy* IA methotrexate Brain imaging to document disruption
Day 4	Leucovorin rescue Discharge
Day 5	Granulocyte colony-stimulating factor

Abbreviations: BBBB, blood-brain barrier disruption; IA, intra-arterial; IV, intravenous.

*Between 1982 and 1993, chemotherapy used in combination with methotrexate included etoposide (150 mg/m² IV days 1 and 2) or cyclophosphamide (15 mg/kg IV days 1 and 2) and procarbazine (100 mg orally days 3 through 16; 44 patients). Between 1994 and 2005, etoposide or etoposide phosphate (150 mg/m² IV days 1 and 2) and cyclophosphamide (500 mg/m² IV days 1 and 2) were used (105 patients). Granulocyte colony-stimulating factor was added in 1994. At that time, etoposide or etoposide phosphate replaced oral procarbazine.

rate of episodes per number of procedures. OS and PFS were measured from the first BBBB treatment date to date of first relapse (for PFS), death, or last follow-up. OS and PFS were estimated using Kaplan-Meier estimates. Potential predictors for OS and PFS were assessed by fitting stratified univariate analyses and comparing strata using the log-rank test or the generalized Wilcoxon test (the latter test used when visual comparison of the stratified curves was not consistent with the proportional hazards assumption). Potential predictors of OS and PFS were age (< 60 v ≥ 60 years), KPS (≥ 70 v < 70), Memorial Sloan-Kettering Cancer Center (MSKCC) risk classes (class 1, age < 50 years; class 2, age ≥ 50 years and KPS ≥ 70 ; class 3, age ≥ 50 years and KPS < 70),²⁸ sex, CSF cytology (negative, positive, or atypical/suspicious), whether or not the patient discontinued treatment as a result of an adverse event, whether or not the patient had intraocular lymphoma, and whether or not surgical resection was performed. The MSKCC risk scores are effectively a statistical interaction term (the interaction of age and KPS) that uses age more than and less than 50 years. In our previous report, we used age more than and less than 60 years. Both of these age cut-points were assessed in this report. Multivariable Cox proportional hazards models were also fit using these potential predictors. Variable selection was made using a modified forward-variable selection approach evaluating both changes in the Akaike's information criterion and P values.

RESULTS

Patient Characteristics

One hundred forty-nine patients were treated with BBBB followed by IA methotrexate-based chemotherapy (2,079 procedures). Seventy-four of these patients were included in previous reports.^{21,22} Patient characteristics are summarized in Table 2. Seventy-eight women and 71 men were included. The mean age (\pm SD) at diagnosis was 54.5 years (± 15.5 years); 47.6% were age 60 years or older. Mean

Table 2. Patient Demographics and Clinical Characteristics at PCNSL Diagnosis

Characteristic	No. of Patients	%
No. of patients	149	
Sex		
Male	71	47.6
Female	78	52.4
Age, years		
Mean	54.5	
SD	15.5	
< 60	78	52.4
≥ 60	71	47.6
KPS		
Mean	69.4	
SD	20.3	
≥ 70	86	57.7
< 70	63	42.3
Disease site		
CNS	131	87.9
CNS and intraocular	15	10.1
Intraocular only	3	2.0
CSF cytology		
Negative	96	64.4
Atypical/suspicious	14	9.4
Positive	11	7.4
Unknown	28	18.8
Surgical resection		
No	88	59.1
Yes	61	40.9
Vitrectomy		
No	138	92.6
Yes	11	7.4

Abbreviations: PCNSL, primary CNS lymphoma; KPS, Karnofsky performance score; SD, standard deviation.

baseline KPS was 69.4 (± 20.3). Sixty-one patients had surgical resection as part of their diagnostic regimen, and 27 patients had started chemotherapy at outside centers and then were referred to a BBB consortium facility for treatment within 90 days of diagnosis. Twenty-five patients had positive CSF for lymphoma cells or atypical cells. The number of patients treated at each center ranged from eight to 104.

Outcomes

The 149 patients received a median of 16 IA/BBBD treatments (eight monthly courses). This resulted in clinical and radiographic CR in 86 patients and partial response in 36 patients (overall response rate, 81.9%). Stable disease was documented in 8.1% and progressive disease in 3.4%. Ten patients (6.7%) were not assessable/unknown. Stratified by age, the response rate was 83.3% for patients younger than 60 years and 80.3% for patients ≥ 60 years. Patients with baseline KPS ≥ 70 had a response rate of 82.6% and patients with KPS less than 70 had a response rate of 81.0%.

Fifty-six patients (37.6%) had no evidence of disease progression at last follow-up, whereas 93 patients (62.4%) experienced disease progression. Median PFS was 1.8 years (95% CI, 1.3 to 2.8 years); 5-year PFS was 31% and 7-year PFS was 25% (Fig 1). KPS ≥ 70 ($P = .0007$, Wilcoxon test) and MSKCC risk class ($P < .0001$, Wilcoxon test) were significant predictors of PFS. Age younger than 60 years ($P = .32$, Wilcoxon test), sex ($P = .64$, Wilcoxon test), CSF

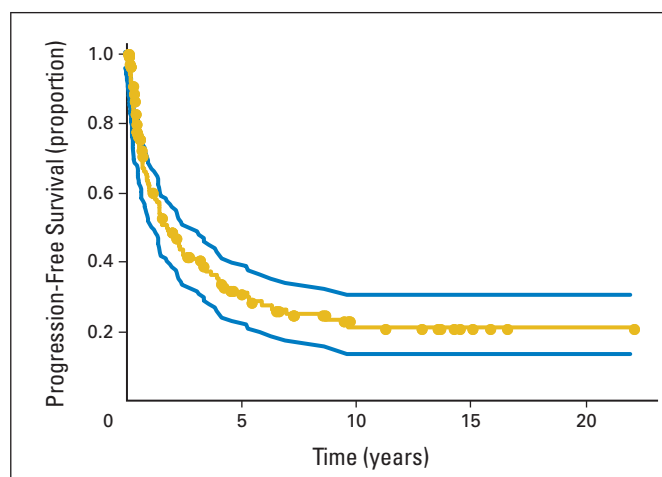


Fig 1. Progression-free survival (yellow line; median, 1.8 years; 95% CI, 1.3 to 2.8 years) from date of first intra-arterial/blood-brain barrier disruption treatment (149 patients, 93 have experienced disease progression) with 95% CI (blue lines). Symbols on lines indicate censored observations.

cytology ($P = .28$, Wilcoxon test), discontinuation owing to complications ($P = .24$, Wilcoxon test), intraocular disease ($P = .90$, Wilcoxon test), and surgical resection ($P = .78$, Wilcoxon test) were not significant predictors.

Ninety-three patients experienced relapse, with the longest after 9.7 years. The site of first relapse was CNS only (73 patients, 49.0%), CNS and intraocular (nine patients, 6.0%), and intraocular only (two patients, 1.3%). Nine patients (6.0%) experienced relapse systemically.

Ninety-six patients (64.4%) have died. Median OS was 3.1 years (95% CI, 2.2 to 5.0 years), with 41% estimated 5-year survival and 25% estimated 8.5-year survival (Fig 2). Age younger than 60 years ($P = .0019$, log-rank test), KPS ≥ 70 ($P < .0001$, log-rank), MSKCC risk classes ($P < .0001$, log-rank test), and sex ($P = 0.039$, Wilcoxon test) were significant predictors for OS. CSF cytology ($P = .93$, Wilcoxon test), discontinuation owing to complications ($P = .92$, Wilcoxon test), intraocular disease ($P = .76$, Wilcoxon test), and surgical

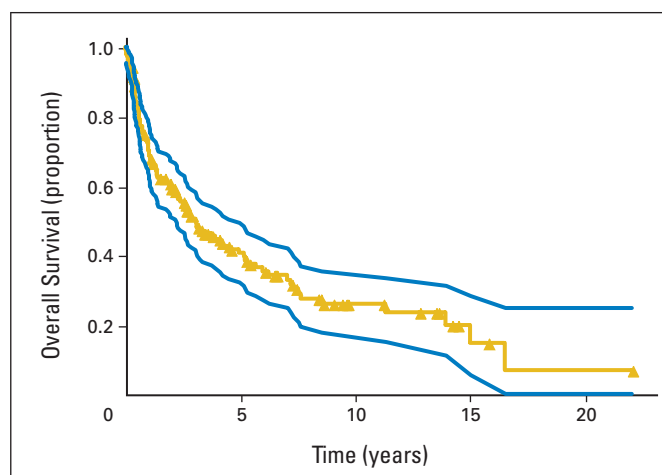


Fig 2. Overall survival (yellow line; median, 3.1 years; 95% CI, 2.2 to 5.0 years) from date of first intra-arterial/blood-brain barrier disruption treatment (149 patients, 96 deaths) with 95% CI (blue lines). Symbols on lines indicate censored observations.

resection ($P = .72$, Wilcoxon test) were not significant predictors. Patients younger than 60 years ($n = 78$) had a median OS of 5.2 years and a 5-year survival rate of 52%; patients ≥ 60 years of age had median OS of 2.2 years and a 5-year survival rate of 30% ($P < .0019$). A plateau in OS was seen at 8.5 years in patients younger than 60 years, suggesting that some of these 13 patients may have achieved a "cure."

The best predictive model for OS included MSKCC class 3 (age ≥ 50 years and KPS < 70 ; hazard ratio = 9.08; $P < .0001$), age ≥ 60 years with KPS less than 70 (hazard ratio = 0.150; $P < .0001$), and age older than 60 years (hazard ratio = 2.39; $P = .0008$). To understand these interactions of age with KPS, all combinations of age younger than 50, age 50 to 60, and age ≥ 60 years and KPS less than 70 and ≥ 70 were fit in one model. The difference among these six combinations was highly significant ($P < .0001$). Visual inspection of the survival curves and improvement in model fit (based on Akaike's information criterion) suggested three risk groups: low risk (age < 60 years and KPS ≥ 70), moderate risk (age < 50 years with KPS < 70 or age ≥ 60 years), and high risk (age 50 to 60 years and KPS < 70 ; Fig 3A). Estimated hazard ratios were 3.24 (95% CI, 1.92 to 5.47) and 11.63 (95% CI, 5.33 to 25.37) for the moderate- and high-risk groups, respectively. Median OS for these three risk groups were 13.9 years (95% CI, 5.2 years to not reached) for the low risk group, 2.3 years (95% CI, 1.3 to 3.1 years) for the moderate risk group, and 0.6 years (95% CI, 0.3 to 0.9 years) for the high-risk group. Similar analyses for PFS also identified three risk categories (albeit with different groups): low (age 50 to 60 years with KPS ≥ 70 or age < 50 years), moderate (age ≥ 60 years), and high (age 50 to 60 years with KPS < 70 ; Fig 3B). Estimated hazard ratios were 1.91 (95% CI, 1.19 to 3.06) and 10.01 (95% CI, 4.61 to 21.75) for moderate and high risk, respectively.

When separately analyzed, the off-protocol patients ($n = 18$) had lower KPS and were older than the on-protocol patients ($n = 131$). The 18 off-protocol patients had higher mean MSKCC risk scores, shorter median OS (1.02 years, 95% CI, 0.37 to 3.75; v 3.24 years, 95% CI, 2.28 to 5.29), shorter median PFS (0.62 years, 95% CI, 0.18 to 1.99; v 2.23 years, 95% CI, 1.43 to 3.45), and a lower rate of CR than the on-protocol patients.

Eighty-seven (90.6%) of the 96 deaths occurred more than 30 days after BBBB/IA. Forty-six patients (47.9%) died as a result of CNS lymphoma progression. Systemic recurrence was the cause of death in nine patients (9.4%). Three patients (3.1%) died as a result of other toxicity such as respiratory complications, five patients (5.2%) died as a result of CNS toxicity, seven patients (7.3%) died as a result of other causes such as cardiac disease, and in 17 patients (17.7%), the cause of death was unknown.

Nine (9.4%) of the 96 deaths occurred less than 30 days after BBBB/IA. One patient died within 48 hours; autopsy showed a pulmonary embolism. Eight patients died 3 to 30 days after BBBB/IA. Four of these patients died of infection, and four patients died from complications related to carotid dissection, myocardial infarction, heart failure, and unknown cause (one each).

Treatment-Related Complications

A total of 697 complications were identified during 2,079 BBBB procedures (33.5%). The complications are summarized in Table 3. The most frequent complication was periprocedural focal seizures occurring in 50 patients (33.6%; 9.2% of procedures). The majority of these occurred during barrier disruption and chemotherapy infusion, were aborted with IV barbiturates, and resulted in no permanent

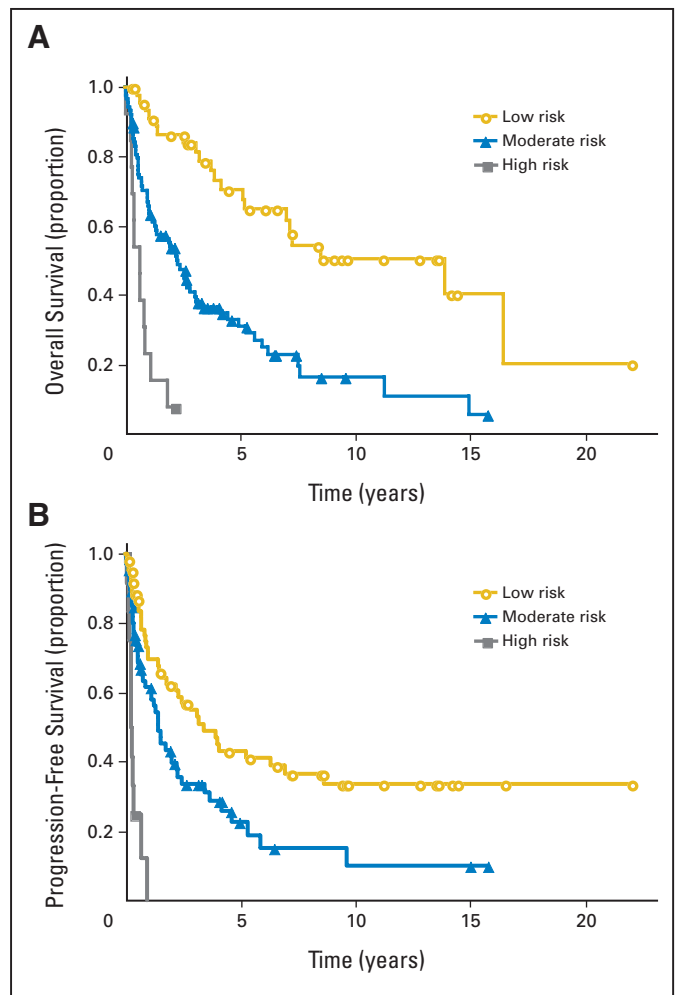


Fig 3. (A) Overall survival according to proposed risk groups. Survival from date of first intra-arterial/blood-brain barrier disruption treatment stratified by age and Karnofsky performance score (KPS). Low risk, age younger than 60 years with KPS ≥ 70 (47 patients); moderate risk, age older than 60 years with any KPS or age younger than 50 years with KPS less than 70 (89 patients); and high risk, age 50 to less than 60 years with KPS less than 70 (13 patients). Symbols on lines indicate censored observations. (B) Progression-free survival according to proposed risk groups. Progression-free survival from date of first intra-arterial/blood-brain barrier disruption treatment stratified by age and KPS. Low risk, age 50 to less than 60 years with KPS greater than 70, or age less than 50 years with any KPS (65 patients); moderate risk, age ≥ 60 years with any KPS (71 patients); and high risk, age 50 to less than 60 years with KPS less than 70 (13 patients). Symbols on lines indicate censored observations.

neurologic dysfunction or uncontrolled seizures. Patients who experienced seizures had an increased likelihood to seize during subsequent procedures (191 seizures occurred in 50 patients; median of three seizures per patient). The overall rate of procedural morbidity is 327 events (15.7% of procedures). However, if focal seizures are excluded,²⁹ there were 136 (6.5%) of 2,079 events. Clinical strokes occurred in 11 patients (7.4%); four patients were left with permanent neurologic deficits. The estimated risk of permanent neurologic deficit is 0.2% per IA/BBBB procedure.

Chemotherapy toxicity and underlying malignant condition-related complications accounted for 370 events (17.8%). Hematologic abnormalities were the most common presentation: RBC transfusions (3.6% of procedures) and granulocytopenic fever (2.8%). These patients had a hypercoagulable tendency with a 2.6% incidence of deep

Table 3. Complications Summary

Event	No. of Patients	%	No. of Episodes	Incidence (% of BBBD procedures)*
Total	149		697	33.5
BBBD procedure-related				
Periprocedural seizure†	50	33.6	191	9.2
Temporary neurologic deficit	27	18.1	39	1.9
Ophthalmologic	25	16.8	25	1.2
Carotid or vertebral artery injury‡	16	10.7	22	1.1
Obtundation > 24 hours§	15	10.1	22	1.1
Periprocedural dysrhythmia requiring intervention	12	8.0	25	1.2
Clinical stroke	11	7.4	16	0.8
Permanent neurologic deficit	4	2.7	4	0.2
Urethral tear with bleeding	2	1.3	2	0.1
Pneumothorax	2	1.3	2	0.1
Respiratory arrest	1	0.7	1	0.0
Femoral arterial thrombosis	1	0.7	2	0.1
Death within 48 hours	1	0.7	1	0.0
Chemotherapy/malignancy-related				
RBC transfusion required	43	28.9	75	3.6
Granulocytopenic fever	40	26.8	59	2.8
Deep vein thrombosis	34	22.8	43	2.1
Septicemia with neutropenia	33	22.2	42	2.0
Septicemia, nongranulocytopenic	31	20.8	41	2.0
Pneumonia	27	18.1	32	1.5
Pulmonary embolus	11	7.4	11	0.5
Platelet transfusion required	10	6.7	13	0.6
Delayed orthopedic	10	6.7	10	0.5
Death within 30 days	8	5.4	8	0.4
Gastrointestinal bleeding	7	4.7	8	0.4
Dementia	2	1.3	2	0.1
Acute myelogenous leukemia	1	0.7	1	0.0

Abbreviation: BBBD, blood-brain barrier disruption.

*Total number of BBBD procedures is 2,079.

†Primarily focal motor seizures without clinical sequelae (see text for details).

‡The most common arterial injury that occurs during BBBD is a subintimal tear. This complication is usually asymptomatic and is noticed during fluoroscopy of the carotid and vertebral arteries.

§Approximately 10% of patients have decreased level of consciousness after BBBD. When this complication occurs, the patients are treated with dexamethasone and usually return to baseline neurologic status within 48 hours.

||Eleven patients had a clinical stroke. Four of these patients (2.7%) had a residual permanent neurologic deficit.

vein thrombosis or pulmonary embolism periprocedurally. Twenty-four patients (16.1%) discontinued the 12-month regimen because of complications; 11 patients discontinued treatment because of secondary infections.

DISCUSSION

Data from three multicenter PCNSL trials that used chemotherapy (high-dose IV methotrexate) alone (New Approaches to Brain Tumor Therapy,³⁰ German Cancer Society Neuro-Oncology Working Group (NOA) 03,³¹ and European Organisation for Research and Treatment of Cancer [EORTC] 26952,³²) are summarized in Table 4. Our results with IA methotrexate/BBBD demonstrated comparable if not superior outcomes to high-dose IV methotrexate used in the other three multicenter trials.

Similarly, the results of Radiation Therapy Oncology Group 93-10³³ and EORTC 20962³⁴ are summarized in Table 4. Both of these trials used combination chemotherapy and brain irradiation. IA methotrexate-based BBBD achieved similar results without the neurocognitive sequelae associated with brain irradiation.³⁵ Caution must

be exercised, as definitive conclusions cannot be drawn when comparing our results with those of other multicenter nonrandomized clinical trials of newly diagnosed patients with PCNSL. Nonetheless, we feel that summarizing results obtained from the other multicenter studies, as we have done in Table 4, may be of interest to clinicians. Given the rarity of PCNSL and the limited number of institutions currently trained in BBBD, a randomized PCNSL trial using BBBD as one arm is currently not possible.

Cognitive outcomes were not available for all patients in our series; however, a subset of these patients have been evaluated as part of other published series.^{11,21,22,35-39} Neuropsychologic assessments include a comprehensive test battery conducted by neuropsychologists. Results revealed cognitive improvement or preservation in the majority of patients relative to pretreatment status at follow-up, between 1 to 7 years after achieving CR.^{11,21,22,35-39} Further evaluation of neurocognitive outcomes in long-term survivors is underway (L. Maron, personal communication, July 2008).

Toxicity in BBBD-treated patients is generally manageable. However, the treatment delivery regimen is complex and should be undertaken only by trained teams at centers where neuro-oncology,

Table 4. Multicenter Studies of Newly Diagnosed PCNSL

Study	No. of Patients	RR (CR + PR; %)	PFS (months)		OS (months)	
			Median	95% CI	Median	95% CI
NABTT 96-07, ³⁰ high-dose methotrexate	25	74	12.8		Not reached (> 23)	
NOA-03, ³¹ high-dose methotrexate	37	35	10		25	
EORTC 26952, ³² high-dose methotrexate	50 (> 60 years old)	48	6.8	3.4 to 10.6	14.3	6.2 to 42
RTOG 93-10, ³³ high-dose methotrexate plus WBRT	102	94	24		36.9	
EORTC 20962, ³⁴ high-dose methotrexate plus WBRT	52 (< 65 years old)	81	—		46	
BBBD consortium, current study						
Total patients	149	81.9	21.3	15.1 to 34.0	37.1	27.0 to 59.5
Age < 60 years	78	83.3	29.8	12.2 to 49.1	61.9	34.2 to 167.3
Age ≥ 60 years	71	80.3	17.6	10.6 to 27.6	26.6	14.5 to 37.1

Abbreviations: PCNSL, primary CNS lymphoma; RR, response rate; CR, complete response; PR, partial response; PFS, progression-free survival; OS, overall survival; NABTT, New Approaches to Brain Tumor Therapy; NOA, German Cancer Society Neuro-Oncology Working Group; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group; WBRT, whole-brain radiation; BBBD, blood-brain barrier disruption.

interventional neurosurgery/neuroradiology, neuroanesthesia, and experienced oncology nursing are available.

Potential predictors of OS and PFS are combinations of age and KPS. Other potential predictors were not statistically significant when added to these models, and the hazard ratios for the moderate and high-risk groups were not changed when these other potential predictors were added. We also assessed MSKCC risk classes, but not the International Extranodal Lymphoma Study Group score (serum lactate dehydrogenase and CSF protein were not regularly available).⁴⁰ Comparisons of multivariable models suggested that, in this case series, neither MSKCC risk categories nor age younger than 60 or ≥ 60 years and KPS less than 70 or ≥ 70 were adequate predictors. Six age-KPS combinations were fit and then grouped into three risk categories. The high-risk group (age 50 to 60 years and KPS < 70) was the likely reason for this interaction. This high-risk group included only 13 patients and may reflect random, small subgroup variation (albeit a group with markedly poor OS and PFS). Many of these 13 patients had numerous premorbid conditions or concomitant complications unrelated to treatment (eg, one patient died secondary to spinal cord injury complications after a fall). Drawing any specific conclusions about this small subset of patients is risky and may be unnecessary. These risk groups are not intended to represent general risk categories (such as MSKCC or International Extranodal Lymphoma Study Group) but merely describe outcomes in this series.

Another potential confounder in this series is the small number of patients treated off-protocol at participating institutions. If we restrict the series to only on-protocol patients, the median OS increases slightly from the full series (from 3.1 to 3.2 years) and the median PFS increases (from 1.8 to 2.2 years). Even though the inclusion of off-protocol patients negatively impacts the efficacy reported in this series, we feel that their inclusion is important and more accurately reflects the overall therapeutic results using BBBD in patients with PCNSL.

Currently, systemic diffuse large B-cell lymphoma is treated with chemotherapy in conjunction with rituximab; however, this monoclonal antibody does not routinely cross the BBB and reach malignant lymphoma cells in the CNS.⁴¹⁻⁴⁴ A reasonable approach might be to use a technique such as osmotic BBBD to deliver effective monoclonal antibody/chemotherapy or other novel agents.

In conclusion, we report response rates and OS from a large, multicenter series of newly diagnosed patients with PCNSL treated

with IA methotrexate-based chemotherapy with osmotic BBBD, which confirm our previously reported single-center results.^{21,22} This treatment option resulted in durable tumor control, manageable toxicity, and the potential for deferral of radiation and its associated cognitive compromise.^{11,22,45} BBBD results in enhanced delivery not simply to areas with overtly leaky BBB associated with enhancing tumor, but also to brain and CSF globally by as much as 50- to 100-fold.⁴⁶ The long patient follow-up suggests this is an effective first-line treatment option with a meaningful impact on OS and PFS, as well as neurocognitive status.³⁵

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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